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Immune Thrombocytopenia in Postpolythemic Myelofibrosis

Zwi A. Schreiber*

Division of Hematology, Bronx Lebanon Hospital, Bronx, New York

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INTRODUCTION

Thrombocytopenia is detected in about 22% of patients with idiopathic myelofibrosis (IM) at the time of diagnosis of this disorder [1]. However, as the disease evolves and cytotoxic therapy is instituted, most patients invariably become thrombocytopenic. The thrombocytopenia is the combined result of progressive bone marrow failure on the one hand and increasing splenic pooling and sequestration of platelets on the other [2]. This report concerns a patient with postpolycythemic myelofibrosis and severe thrombocytopenia. Immune destruction was a major factor in producing the thrombocythemia in our patient. Two previous patients with the association of immune thrombocytopenia and myelofibrosis have been described. One patient definitely had systemic lupus erythrematosus (SLE) and immune thrombocytopenia for several years before myelofibrosis was detected [3]. The second patient had idiopathic myelofibrosis, thrombocytopenia, and a positive platelet-associated antibody [4]. Autoimmune phenomena are common in IM patients and manifest by circulating immune complexes, complement activation and the appearance of antinuclear antibodies, anti-DNA antibodies, and rheumatoid factors in serum. A positive direct antiglobulin test on red cells has been reported in up to 19% of patients with IM, some of them having definite hemolytic anemia [4,5]. Similar autoimmune manifestations have been reported in patients with postpolycythemic myelofibrosis, but the incidence is lower than in IM patients [4].

CASE REPORT

F.L., a 55-year-old African-American woman, was admitted on March 5, 1992 because of a 3-month history of weakness, loss of appetite, and a 25-pound weight loss.

Past History

In 1986 she was seen by a hematologist because of an abnormal blood count. The white cell count was 52,000/mm^3, hematocrit was 46%, and the platelet count was 914,000/mm^3. The spleen was not palpable, and a bone-marrow aspiration revealed a hypercellular specimen with myeloid and magakaryocytic hyperplasia. In 1987, a white cell count (WBC) of 44,000/mm^3 was seen, with 76% neutrophils and 24% lymphocytes, hematocrit of 51%, and a platelet count of 780,000/mm^3. Because of possible essential thrombocythemia, she was treated for 6 months with myleran and allopurinol. The subsequent count after myleran treatment was: WBC 13,400/mm^3, hematocrit 52%, and platelet count 189,000/cu mm. In 1988, a diagnosis of polycythemia vera was made when hematocrit rose to 61%. Several phlebotomies were performed, and she was then given oral hydrea for the next 4 months. In 1990, she was given another course of hydrea due to high hematocrit. A blood count done in November, 1991 revealed a white cell count of 6,900/mm^3, hematocrit of 30%, and a platelet count of 115,000/mm^3.

Physical Examination

Physical examination revealed a chronically ill, pale-looking female. She was afebrile, with no palpable lymph nodes, liver, or spleen. There was no joint swelling or tenderness. There were some ecchymotic areas at the sites of the venopunctures in the arms. Otherwise no petechia or ecchymosis were seen.

Laboratory Data

The white cell count was 3,700/mm^3, with 25 neutrophils, 25 bands, 33 lymphocytes, 12 monocytes, and two basophils. Hematocrit was 21.5%, MCV was 88.9, platelets were 8,000/mm^3, and the reticulocyte count was 1.5%. The peripheral smear showed marked anisocytosis and

*Correspondence to: Zwi A. Schreiber, M.D., 1650 Selwyn Ave. 3C, Bronx, NY 10457.

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poikilocytosis. Many ovalocytes and teardrop cells were seen, as well as polychromasia and basophilic stippling. Also, nucleated red blood cells and dwarf megakaryocytes were noted on the peripheral film. The platelets were markedly decreased. The serum vitamin B_{12} level was 1,623 pg/ml, folate 3.2 ng/ml, ferritin 386 ng/ml, iron 121 ng/ml, and TIBC 125 ng/ml. The direct Coombs' test was repeatedly negative. The following blood chemistry values were abnormal: total bilirubin of 1.7 mg/dl, direct bilirubin of 0.9 mg/dl, LDH of 389 IU/l, and uric acid of 12.2 mg/dl. Total protein was 6.9 g/dl with an albumin level of 3.9. g/ml. Urinalysis was normal except for 30 mg/dl of protein. Prothrombin time was 17/12 sec, and partial thromboplastin time was 31/28 sec. Platelet-associated Ig-G and complement level (C3), done by an immunofluorescent method [6,7], was markedly positive. The ratio of the amount of immunoglobulin G coating the patient's platelets over the control platelets was 15.8. The ratio of the complement (C3) coating the patient's platelets over the control platelets was 27.1. This was repeated 1 month later with similar results. The Philadelphia chromosome DNA rearrangement was not detected using the BCR-3 probe and the BG-1, BG-2, and Xba restriction enzymes in a Southern blot hybridization procedure [8]. Bone-marrow aspiration yielded a dry tap. Bone-marrow biopsy revealed complete replacement by extensive fibrosis. A small hypocellular segment with less fibrosis displayed a few mononuclear cells and scattered, trapped megakaryocytes. Scant myeloid elements with eosinophils were also seen. The patient refused HIV antibody testing, but the CD4 helper cell count was 812/mm^3, and the CD8 count was 928/mm^3 with a CD4/CD8 ratio of 0.9. The rheumatoid factor was 49 IU/dl (normal), the antinuclear antibody was positive at a titer of 1:40, and the DNA antibody was 285 U/dl (borderline value). The serum complement C3 was 86 mg/dl (normal, 55–120 mg/dl). During this admission an abdominal CT scan revealed a mildly enlarged spleen, which was subsequently confirmed by an abdominal sonogram.

Clinical Course

The patient was transfused with packed red blood cells and started on a daily oral dose of 40 mg of prednisone as well as 100 mg of pyridoxin. Over the next 2 months, hematocrit was stabilized at 25%, but the patient had persistent severe thrombocytopenia in the range of 10,000–20,000/mm^3. There was no clinical evidence of bleeding; the patient's appetite improved and she started gaining weight. On May 24, 1992 she expired suddenly at home. No autopsy was performed.

DISCUSSION

The patient reported here had postpolycythemic myelofibrosis, associated with severe thrombocytopenia. The thrombocytopenia was due to a combination of immune destruction, hypoproliferation from markedly fibrotic bone marrow, and pooling in a mildly enlarged spleen. The thrombocytopenia responded minimally to oral steroids. Ten weeks after her last hospital admission, the patient expired suddenly at home. This probably was due to a cardiovascular event. Cardiovascular complications and mortality have been reported in a high proportion of IM patients [1]. The patient had no history of joint disease, rash, or previous renal disease. Although the DNA antibody was borderline, the patient did not fulfill the criteria for SLE, as formulated by the American Rheumatism Association [9].

Thrombocytopenia is detected in about 22% of IM patients at diagnosis, and is commonly present in the advanced stage of the disease [2]. In a review of 80 patients with myelofibrosis, Hasselbalch [5] noticed that thrombocytopenia was more prevalent in patients with acute myelofibrosis. Acute myelofibrosis is characterized by pancytopenia, the appearance of primitive blast cells in the peripheral blood, hypercellular bone marrow with increased blasts and atypical megakaryocytes, and a normal-sized spleen [10]. In the patient reported here, there is no evidence of acute myelofibrosis. When platelet kinetic studies were performed in patients with IM, it was demonstrated that they had a fourfold increase in platelet production, a marked increase in splenic pooling, and somewhat decreased platelet survival [11]. These platelet kinetic studies were done on 7 patients with IM, who had markedly enlarged spleens, but no thrombocytopenia.

However, other authors mention that the thrombocytopenia that occurs in IM is due to hypoproliferation from fibrotic bone marrow in addition to excessive splenic pooling [2]. This disparity on the pathogenesis of thrombocytopenia in IM may be explained by virtue of the studies having been done at different stages of the disease. Immune destruction as a mechanism of thrombocytopenia in myelofibrosis has been mentioned only twice before. One patient who definitely had immune thrombocytopenia associated with SLE for 9 years was subsequently found to have myelofibrosis [3]. Another patient with IM and thrombocytopenia had a positive platelet-associated antibody test [4]. Our patient had postpolycythemic myelofibrosis associated with immune thrombocytopenia and a markedly positive platelet-associated Ig-G and complement (C3) test. Recent studies have demonstrated that almost all platelet IgG is contained within the secretory alpha granules. A very small fraction of the normal platelet IgG, $<1\%$ of the total, is on the platelet surface [12]. Platelet-surface IgG is consistantly increased in patients with ITP. The assumption that platelet-surface IgG represents antibodies is supported by the high frequency of detection of specific antibodies to platelet glycoprotein IIb-IIIa or to platelet glycoprotein Ib-IX in immune thrombocytopenia [12–14]. Platelet-surface IgG in ITP

patients appears to mediate platelet binding to monocytes, consistent with an in vivo mechanism for platelet destruction [12]. Also, many patients with ITP have been demonstrated to have increased concentrations of IgM, an abnormality that may promote complement mediated platelet destruction. Kelton et al. [15] and Mueller-Eckhardt et al. [16] reported increased levels of platelet-associated IgG in thrombocytopenic patients, even where the thrombocytopenia was not due to immune destruction. Data collected by George [12] from six series revealed that patients with ITP had an 18–26-fold increase in platelet-surface IgG as compared to normal controls. On the other hand, patients with thrombocytopenia due to decreased production had only a sixfold increase in platelet-surface IgG. In thrombocytopenia due to immune destruction, large amounts of IgG are coating the platelets in contrast to thrombocytopenia due to decreased production, when platelet-surface IgG is increased only minimally. Possibly, this could explain the reports of Kelton et al. [15] and of Mueller-Eckhardt et al. [16]. In our patient, the platelet-surface IgG measured by an immunofluorescent method [6,7] was increased 15-fold over controls. The amount of complement on the surface of the patient's platelets was 27-fold greater than controls. This large increase in platelet-surface IgG and complement in our patient suggests that immune destruction was the major cause of the thrombocytopenia, rather than decreased production from fibrotic bone marrow.

The etiology of bone-marrow fibrosis in IM is not clear. As for the other myeloproliferative diseases, cytogenetic and enzymatic studies have shown that IM is a clonal proliferation of a multipotent stem cell [1,17]. However, these studies have also demonstrated that the bone-marrow fibrosis in IM patients is a reactive process that is the result of functional and kinetic stimulation of nonclonal fibroblasts by growth factors shed from clonal megakaryocytes [18].

A suggestion that myelofibrosis can have an autoimmune etiology comes from the reported high level of serum immune complexes in up to 80% of IM patients. In addition, recent studies of IM patients reported an incidence of up to 19% of patients with a positive direct Coombs' test. Some of these patients had evidence of hemolysis [5]. Rondeau et al. [4] compared autoimmune abnormalities in IM patients, polycythemia vera patients with myelofibrosis, and polycythemia vera patients without myelofibrosis. The incidence of autoimmune abnormalities was high in IM patients, and somewhat lower in patients with polycythemia vera associated with myelofibrosis. However, patients with polycythemia vera without myelofibrosis had minimal evidence of autoimmune abnormalities. It is remarkable that only 3 patients have been reported with the association of immune thrombocytopenia and myelofibrosis. The thrombocytopenia in patients with myelofibrosis is often attributed either to hypoproliferation from a fibrotic bone marrow or to splenic pooling. Immune destruction of platelets as a mechanism of thrombocytopenia in myelofibrosis could be more common than reported.

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